

Study of the transformations of micro/nano-crystalline acetaminophen polymorphs in drug-polymer binary mixtures

Article (Published Version)

Maniruzzaman, Mohammed, Lam, Matthew, Molina, Carlos and Nokhodchi, Ali (2017) Study of the transformations of micro/nano-crystalline acetaminophen polymorphs in drug-polymer binary mixtures. *AAPS PharmSciTech*, 18 (5). pp. 1428-1437. ISSN 1530-9932

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/62365/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

Copyright and reuse:

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Research Article

Theme: Preparation of Nano and Micro-structures for Drug Delivery

Guest Editors: Dr. Z Ahmad and Prof. M Edirisinghe

Study of the Transformations of Micro/Nano-crystalline Acetaminophen Polymorphs in Drug-Polymer Binary Mixtures

Mohammed Maniruzzaman,^{1,3} Matthew Lam,¹ Carlos Molina,¹ and Ali Nokhodchi^{1,2,3}

Received 11 May 2016; accepted 20 July 2016

Abstract. This study elucidates the physical properties of sono-crystallised micro/nano-sized acetaminophen/paracetamol (PMOL) and monitors its possible transformation from polymorphic form I (monoclinic) to form II (orthorhombic). Hydrophilic Plasdane® S630 copovidone (S630), N-vinyl-2-pyrrolidone and vinyl acetate copolymer, and methacrylate-based cationic copolymer, Eudragit® EPO (EPO), were used as polymeric carriers to prepare drug/polymer binary mixtures. Commercially available PMOL was crystallised under ultra sound sonication to produce micro/nano-sized (0.2–10 microns) crystals in monoclinic form. Homogeneous binary blends of drug-polymer mixtures at various drug concentrations were obtained *via* a thorough mixing. The analysis conducted *via* the single X-ray crystallography determined the detailed structure of the crystallised PMOL in its monoclinic form. The solid state and the morphology analyses of the PMOL in the binary blends evaluated *via* differential scanning calorimetry (DSC), modulated temperature DSC (MTDSC), scanning electron microscopy (SEM) and hot stage microscopy (HSM) revealed the crystalline existence of the drug within the amorphous polymeric matrices. The application of temperature controlled X-ray diffraction (VTXRPD) to study the polymorphism of PMOL showed that the most stable form I (monoclinic) was altered to its less stable form II (orthorhombic) at high temperature (>112°C) in the binary blends regardless of the drug amount. Thus, VTXRD was used as a useful tool to monitor polymorphic transformations of crystalline drug (e.g. PMOL) to assess their thermal stability in terms of pharmaceutical product development and research.

KEY WORDS: monoclinic; nano-sized crystals; orthorhombic; sono-crystallisation; variable temperature XRPD.

INTRODUCTION

‘Polymorphism’ generally referred as the ability of a crystalline material to exist in two or more crystalline forms is considered a pivotal part of the crystallisation processes (1, 2). A metastable state of the polymorphs which may not necessarily be obtained easily can accelerate physicochemical and mechanical properties of a drug substance compared to that of the marketed or its naturally occurred counter stable form (1). Moreover, different polymorphic forms may result on significant changes in the solubility and dissolution rates of an active entity (1). By definition, crystalline polymorphs are those crystal lattice in which

the crystalline components represent different and discrete phases from a thermodynamic viewpoint.

The current demand for micro/nano-material various applications in medical and pharmaceutical industry especially in drug delivery has triggered the research in organic crystal engineering and development (3, 4). Crystal engineering is particularly important for the development of pharmaceutical molecules in the context of improved drug delivery or bio-labelling/bio-sensing (5, 6). Micronising of molecular crystals has also become an emerging approach mainly in the development of different water insoluble drugs by enhancing the dissolution rates (7, 8). Interestingly, despite the unique physicochemical properties of the molecular crystals, majority of the reported studies have primarily focused on the solubility aspects whilst other applications such as mechanical properties have been relatively unexplored in pharmaceutical research and developments. There is an immense need to explore the potential of crystal engineering to enhance the physical/mechanical properties of drug candidates (e.g. paracetamol). It has been seen that the implementation of sono-crystallization—the use of ultrasound to facilitate crystallisation (9)—can produce micro to

¹Pharmaceutics Research Laboratory, School of Life Sciences, University of Sussex, Arundel Building, Falmer, Brighton BN1 9QG, UK.

²Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

³To whom correspondence should be addressed. (e-mail: M.Maniruzzaman@sussex.ac.uk; A.Nokhodchi@sussex.ac.uk)

nano-meter-sized crystals with improved mechanical properties. Moreover, it will be of significant interest in crystal engineering and science to monitor the stability of the polymorphic forms or the transformations of these sono-crystallised micro/nano-sized drug crystals.

Paracetamol (PMOL) exists as a white crystalline powder is used as analgesic pain reliever (10). It is sparingly soluble in water (~12.78 mg/ml), and it exhibits multi-polymorphic forms such as monoclinic, orthorhombic and a rarely occurred meta or less stable form with less stability and melting points (11, 12). These forms are also known as forms I, II and III, respectively. Thus, PMOL serves an excellent model drug candidate to study the effects of manufacturing techniques and the subsequent conversions on its crystal forms (1, 11). Also, the glass transition temperature of PMOL at 25°C makes it an interesting system (11). The crystallisation technique and process to engineer the micronised (or nano-sized) crystals of PMOL may provide a useful mean for the characterisation and evaluations of the physico-chemical properties of the pharmaceutical dosage forms. Temperature variable X-ray powder diffraction (VTXRPD) analysis has already been used as a powerful tool to characterise the polymorphism of pharmaceutical crystalline drugs and their stability as a function of increasing temperature (13, 14). In one of our previous study, the effect of temperature on the transformation of PMOL crystal was studied by implementing VTXRD as a predictive tool during the HME processing (15). However, the effect of crystal engineering, e.g. sono-crystallisation on the polymorphic stability of the PMOL crystals, was not studied.

We report a new case to fabricate micro/nano-sized PMOL crystals and monitor its polymorphic transformation upon heating using a VTXRD method to assess the stability of the manufactured crystals alone or in combination with either hydrophilic vinylpyrrolidone-vinyl acetate polymers (S630) or methacrylate copolymers (EPO).

MATERIALS AND METHOD

Materials

The drug paracetamol (PMOL) was bought from Sigma-Aldrich (Gillingham, UK). Vinylpyrrolidone-vinyl acetate, Plasdone S630 (S630) and Eudragit EPO (EPO) were donated by ISP (Germany) and Evonik Industries (Germany), respectively, and were used as received.

Calculations of Hansen Solubility Parameters (δ)

Solubility parameters (16) were determined for the assessment of the possible miscibility of the drug with two polymers and were determined by utilising the Hoftyzer and van Krevelen method (17) as shown in the equation below:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

where

$$\delta_d = \frac{\Sigma F_{di}}{V_i}, \delta_p = \frac{\sqrt{\Sigma F_{pi}^2}}{V_i}, \delta_h = \frac{\sqrt{\Sigma E_{hi}}}{V_i}$$

i = group contributions in the drug/polymer molecules, δ = solubility parameters, F_{di} = dispersion energy, F_{pi}^2 = molar polarization energy, E_{hi} = hydrogen bonding and V = molar volume.

Preparation of Paracetamol Crystals and Drug-Polymer Binary Mixtures

Excessive amount of PMOL (500 mg) was dissolved in minimal amount of ethanol (3 ml) and stirred with a magnetic stirrer in ambient until all PMOL got completely dissolved in the solvent making the solution completely transparent. The PMOL solution was then poured into n-hexane solution (200 ml) kept in an ultra-sonic bath at 50-kHz frequency (Fisher Chemicals, UK) until sono-crystallised PMOL particles precipitated completely. The precipitation of crystallised PMOL was then isolated by using a vacuum pump and washed with additional n-hexane and kept in oven at 50°C overnight to obtain dry PMOL crystals.

Manufactured crystallised PMOL was mixed with two hydrophilic polymers to investigate the possible drug/polymer miscibility and hence any interactions that may lead to a possible polymorphic transformation. The loadings of PMOL in the formulations were kept between 30 and 60% (w/w) as shown in Table I. Appropriate amount of drug and polymer was mixed in a mortar and pestle prior to a thorough blending in a TF2 Turbula mixture (Switzerland) for 10 min in order to obtain a homogenous drug/polymer binary mixture.

Microscopic Imaging

The surface properties of the bulk drug and the drug/polymer mixtures were evaluated by Stereo-Scan S360 SEM (Cambridge Instruments, UK) at the accelerating voltage of 20 kV. For this purpose of the study, the samples were mounted on an aluminium stub using adhesive carbon tape and were sputter coated with gold. A Leica high-magnification microscope was used to take photographs of the crystalline PMOL particles for the comparison with the commercial drug. The average particle size was determined by investigating an area having at least 200–500 particles of the sono-crystallised PMOL and measuring the diameter by using the scale bar presented in the images.

Thermal Analysis Via DSC and MTDSC

The solid state of the bulk drug, bulk polymers and mixtures of drug/polymers in different ratios was studied by using a differential scanning calorimeter (DSC) 823e manufactured by Mettler-Toledo (Greifensee, Switzerland).

Table I. Formulation Compositions of PMOL and Percentage Crystallinity of PMOL in Various Drug/Polymer Binary Blends

Name	F1	F2	F3	F4	F5	F6
Paracetamol	30	50	60	30	50	60
Eudragit EPO	70	50	40			
Plasdone S630				70	50	40
Crystallinity (%)	28.2	48.2	58.3	27.9	47.7	58.7

Approximately 3–5 mg of samples was weighed and taken in a sealed aluminium pans and heated at 1–10°C/min variable heating rates at the range of 0–220°C under an inert environment (nitrogen). The lids were pierced to allow the release of the excessive pressure generated upon heating. The experimental set-up for conducting the modulated temperature differential scanning calorimetry (MTDSC) was temperature 20 to 150°C (pulse width of 15–30 s), heating rate of 1°C/min and the pulse height at 1–2°C.

HSM Analysis

The thermal analysis of sono-crystallised drug in the formulations was studied using a hot stage microscopy (Olympus BX60 microscope, Olympus Corp., USA) with Insight QE camera (Diagnostic Instruments, USA) that was used to monitor the sample transitions. A FP82HT hot stage controlled by a FP 90 central processor (Mettler Toledo, Columbus, OH) was used to maintain temperatures between 20 and 250°C while a spot advance software (Diagnostic Instruments, Inc.) was utilised to capture the images.

Single X-Ray Crystallographic Study

An appropriately selected single crystal of sono-crystallised PMOL was placed onto a 0.1-mm tip of a glass fibre and placed on a Bruker Apex II CCD diffractometer (Germany). The data collection was performed at 173(2) K using MoK α radiation while the SAINT processing program was utilised for data processing and manipulations. The PMOL crystal structure was extracted and refined by using Bruker SHELXTL.

VTXRPD Analysis

The crystallinity and the possible polymorphic transformation of PMOL were evaluated by using a Bruker D8 Advance (Germany) in theta-theta reflection mode with copper anode. A parallel beam Goebel mirror with 0.2-mm exit slit and LynxEye sensitive detector opening at 3 degrees with 176 active channels was used. Each sample was scanned from 2 to 40 2 θ with a step size of 0.02 2 θ . An Anton Paar TTK450 non-ambient sample chamber was used to achieve the variable temperature with a heating rate of 0.2°C/s. Data collection and interpretations were performed using DiffracPlus and the the EVA V.16 program, respectively (18).

RESULTS AND DISCUSSION

Drug/Polymer Miscibility (Hansen Solubility Parameters)

The drug/polymer miscibility was estimated by correlating the energy of mixing from inter- and intra-molecular interactions of the materials used (drug and polymers) (19). For this purpose, the Hansen parameters (δ) calculated based on the structural orientation of the component informs that the drug-polymers with similar δ values used in a system are likely to interact with each other as matter of being miscible. It has widely been accepted that two compounds are generally treated miscible when $\Delta\delta$ is less than 7 MPa^{1/2} (17, 20). The higher values of $\Delta\delta$ (>7 MPa^{1/2}) between a drug/polymer pair generally indicate an immiscibility.

It has been seen in the literature that the solubility parameters provide a general indication of two components which are generally a drug and a polymer to develop solid drug-polymer mixtures in which drug particles can be dispersed in the polymer matrices. The estimated δ values of PMOL, S630 and EPO are summarised in Table II, where it can be seen that the $\Delta\delta$ of both hydrophilic polymeric carriers and the drug used in the binary systems are less than 7 MPa^{1/2}. This indicates that PMOL is miscible with both S630 and eudragit grade copolymer EPO. The $\Delta\delta$ values observed in both drug/polymer binary systems are less than 7 MPa^{1/2}. Therefore, based on the theoretical calculation, it can be claimed that both polymers are expected to be miscible with the drug used in the binary systems.

Microscopic Imaging

The surface properties of the bulk API and the drug/polymer binary mixtures studied by SEM are shown in Fig. 1a. The micrographs of crystallised PMOL exhibited octahedral shaped crystals representing monoclinic form (2). Similarly, the commercial PMOL revealed similar characteristic monoclinic crystalline structures (data not shown). The surface analysis conducted *via* SEM of all binary mixtures also showed the presence of monoclinic form of PMOL in nano-to micro-scale with both S630 and EPO polymers in all formulations. These findings indicated the presence of crystalline PMOL in its original monoclinic form without any transformations yet. Interestingly, the photographs captured *via* a High-Magnification Leica microscope of both commercial PMOL (un-micronized) and the sono-crystallised PMOL (micronized) revealed significant size differences as shown in Fig. 1b. The average particle size of the commercial PMOL crystals ranged from 50 to 250 μ m (by investigation at

Table II. Hansen Solubility Parameters of PMOL and Polymers Used in the Binary Blends

Sample	δ_d (MPa ^{1/2})	δ_p (MPa ^{1/2})	δ_v (MPa ^{1/2})	δ_h (MPa ^{1/2})	δ (MPa ^{1/2})	$\Delta\delta$
Paracetamol	19.67	7.93	21.20	13.96	25.39	–
Plasdone S630	15.14	0.45	15.15	12.18	19.43	5.96
Eudragit EPO	17.89	0.65	17.89	6.08	18.90	6.49

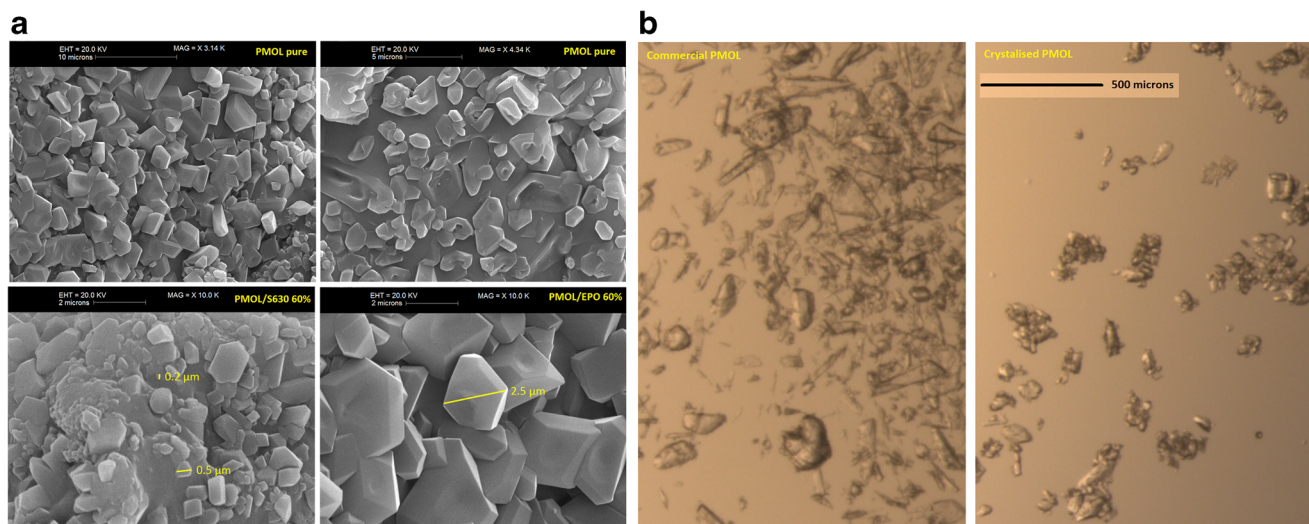


Fig. 1. **a** SEM images of the micro-crystalline PMOL and the formulations; **b** microscopic photographs of commercial PMOL and sonocrystallised PMOL (micro-nano sized)

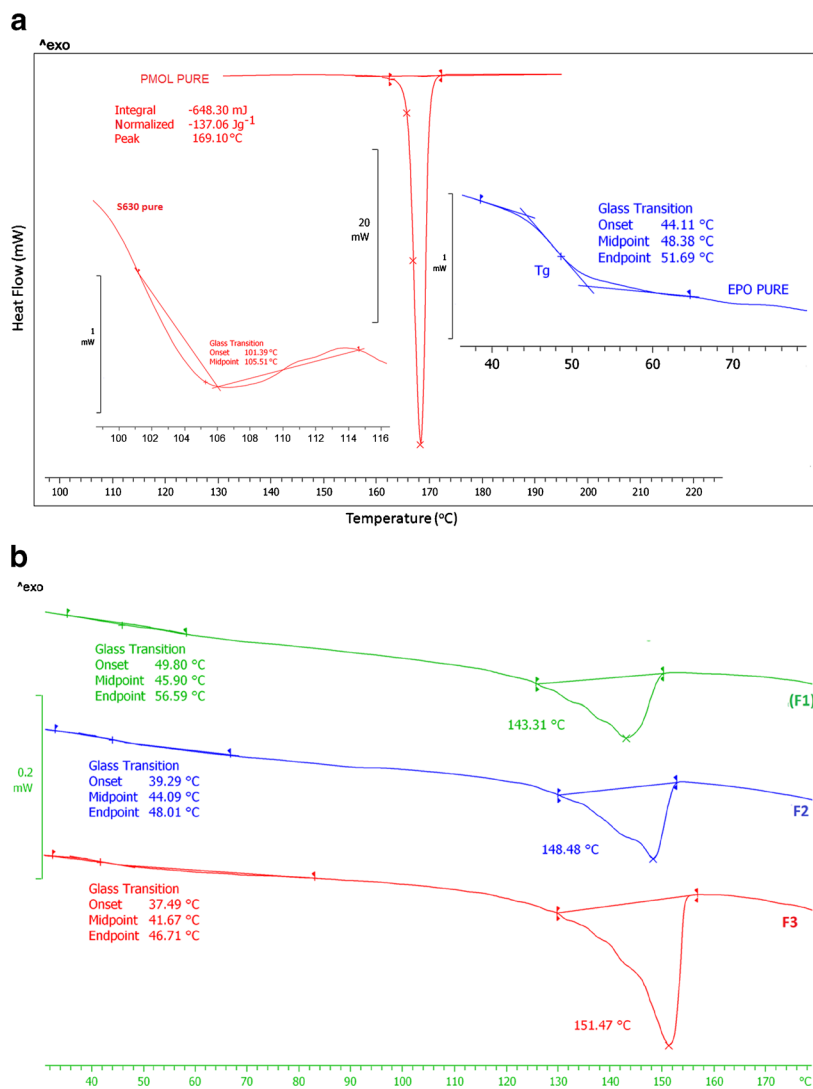


Fig. 2. **a** DSC thermal transitions of bulk PMOL and polymers. **b** DSC thermograms of PMOL/EPO binary systems

Table III. Thermal Transition Summary of Bulk Drug, Polymers and the Drug/Polymer Binary Formulations

Formulations	Glass transition/ enthalpy (°C/ ΔH , Jg ⁻¹)	Melting endotherms/ enthalpy (°C/ ΔH , Jg ⁻¹)
PMOL	24.55	169.1/137.06
S630	105.5	N/A
EPO	48.56	N/A
F1	45.90	143.31/20.49
F2	44.09	148.48/23.83
F3	41.67	151.47/33.81
F4	52.85	137.04/13.27
F5	105.80	131.30/7.20
F6	102.25	123.35/5.50

least 200–500 particles) while the sono-crystallised PMOL (PMOL) showed a particle size ranging from 0.2 to 10 μm . This was also evident in all drug/polymer binary mixtures using two different polymers. The optimised sono-crystallisation approach

produced nano-sized crystals of PMOL which may prove advantageous to enhance the physico-mechanical properties of the very poorly compactible actives such as PMOL. Similar studies have been reported elsewhere (21).

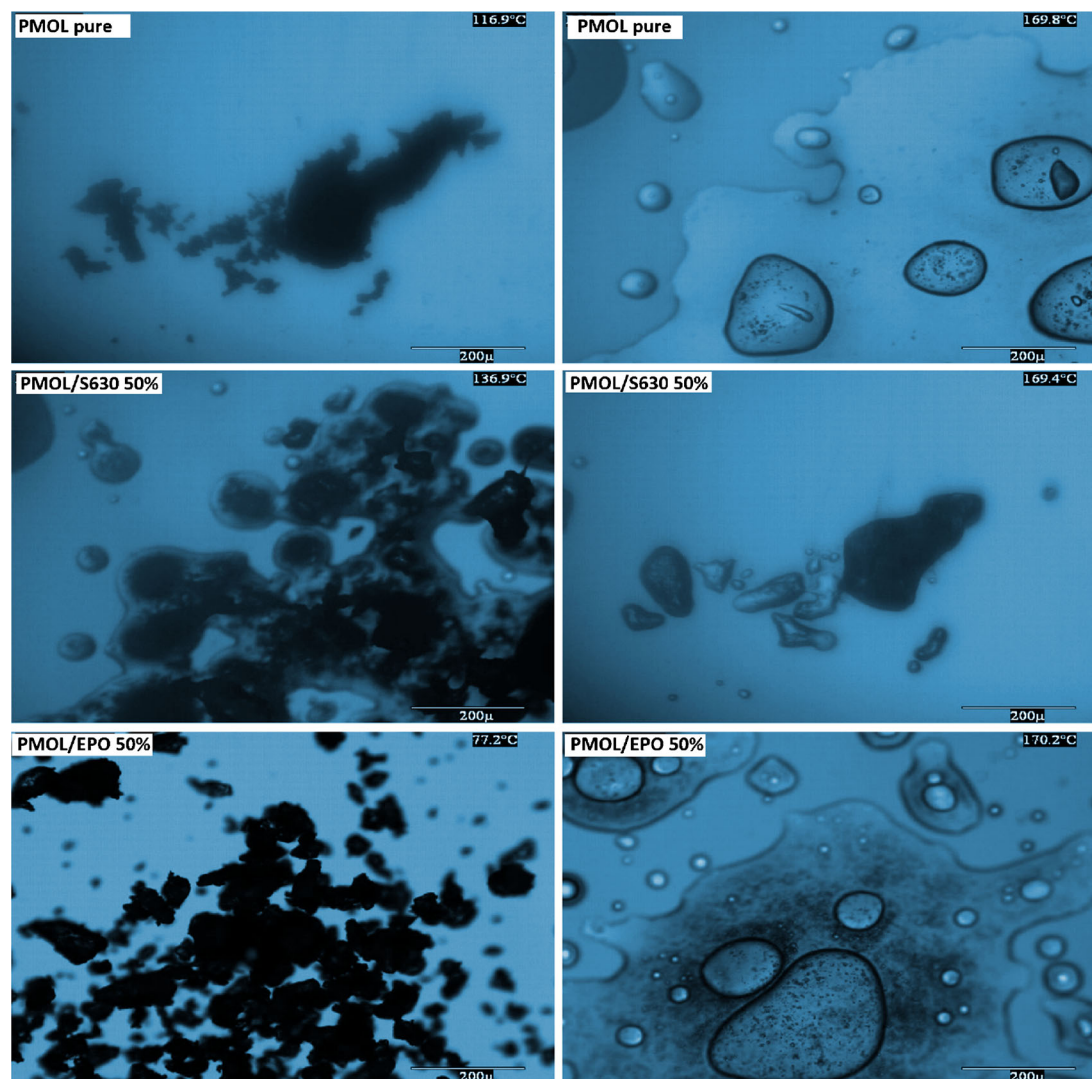


Fig. 3. HSM images of PMOL and PMOL loaded formulations

Thermal Analysis

The thermal transitions of the bulk drug, polymers and the formulations were analysed by DSC. The DSC thermograms of crystallised PMOL showed a sharp transition due to its melting at 169.1°C with an enthalpy ΔH 137.00 J/g. This transition represents the polymorphic form I (monoclinic) (Fig. 2a) and complements the findings from the literature (2, 10, 11). In the case of both polymers, a modulated temperature DSC was used as the conventional DSC thermogram showed enthalpy relaxation peak that overlapped with the glass transition temperatures (T_g s) of the polymers. For methacrylate EPO, an endothermic thermal step change was observed at 48.38°C whilst for S630 at 105.51°C. Both endothermic thermal events correspond to the T_g of the respective amorphous copolymers.

The DSC thermograms of the drug/EPO mixtures (F1-F3) (Table III) showed endothermic thermal transitions at 143–151.57°C at various drug loadings (30–50% w/w ratios) (Fig. 2b). Similarly, all formulations with S630 showed two endothermic thermal transitions as shown in Table III: one

corresponding to the melting of the drug at higher end (123–137°C) and another one at lower end due to the T_g s of the amorphous polymer. From the results, it is quite evident that the shifted melting transitions have become broader compared to those of pure drug indicating the decrease in the crystallinity of PMOL (12). Moreover, this could also possibly be attributed to the drug-polymer interactions in the binary blends. However, the study of volume fraction of PMOL in the formulations has played a pivotal role on the melting temperature of the drug with EPO. The increase in the drug concentration in the formulations resulted in the increase in the melting endotherms (data not shown). In contrast, a different result was observed with the S630 polymer, due to the nature of the polymer and possible drug/polymer interaction strength.

Fragility indicates the degree of viscosity and relaxation time change of a material at its glassy state. The fragility index (m) of strong glasses has typical values of $m < 100$ and weak glasses $100 < m < 200$ (11). In this study, the activation enthalpy and thus the fragility index (m) at the T_g s were estimated by using DSC as expressed in the following

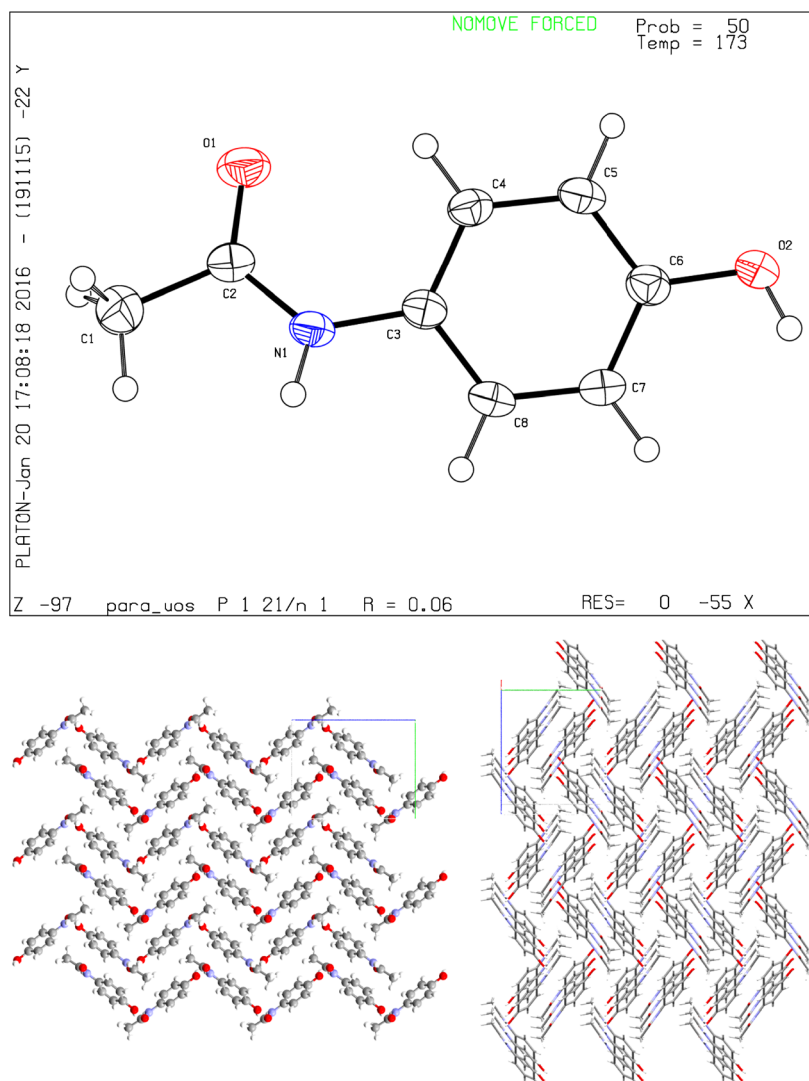


Fig. 4. Single X-ray crystallographic image of PMOL-monoclinic form (stacking)

Transformations of Micro/Nano-crystalline Acetaminophen

equations: where m = fragility index, E_a = activation energy and R = gas constant (22, 23).

$$\ln q_+ = -\frac{E_a}{RT} \quad (2)$$

$$m = E_a / (2.303 * R * T_{gm}) \quad (3)$$

By using Eq. (3), it has been calculated that the crystallised PMOL has a fragility index of 83.8, which is less than that found by Qi *et al.* 86.7 (11). It simply indicates that the PMOL system in this study is a stronger glass compared to that of previously studied amorphous paracetamol. Similarly, the m values calculated for PMOL in PMOL/S630 (F4-F6) formulations are between 97.7 and 188.9 for 30–60% PMOL loadings which indicates that PMOL is neither same as amorphous paracetamol nor crystalline paracetamol form I. Rather PMOL in the formulations upon heating represents more fragile systems (*e.g.* form II) may be stuck together by weak van der Waals forces (11, 23).

Thermal analysis conducted *via* HSM determined the thermal transitions due to the melting of crystalline PMOL within the polymer matrices as a function of heating. Various images of both the bulk drug and drug/polymer binary mixtures taken using HSM are depicted in Fig. 3. As expected, the bulk drug exhibited no thermal changes up to its melting (168°C) complementing the results obtained from the DSC. In the DSC results, there were no thermal events that occurred until about 169.10°C when it melted. Similar to the DSC findings, the drug/polymer binary mixtures displayed minimal drug melting at the heating temperature that reaches 130–140°C and afterward presented a complete melting of the drug crystals present in the polymer matrices (Fig. 3).

Variable X-Ray Powder Diffraction (VTXRPD) Studies

The variable temperature effect on the alteration in the crystal structure of sono-crystallised PMOL was monitored by VTXRPD approach. The results obtained from the XRPD upon heating the samples were recorded for bulk PMOL, PMOL/S630 and PMOL/EPO binary systems.

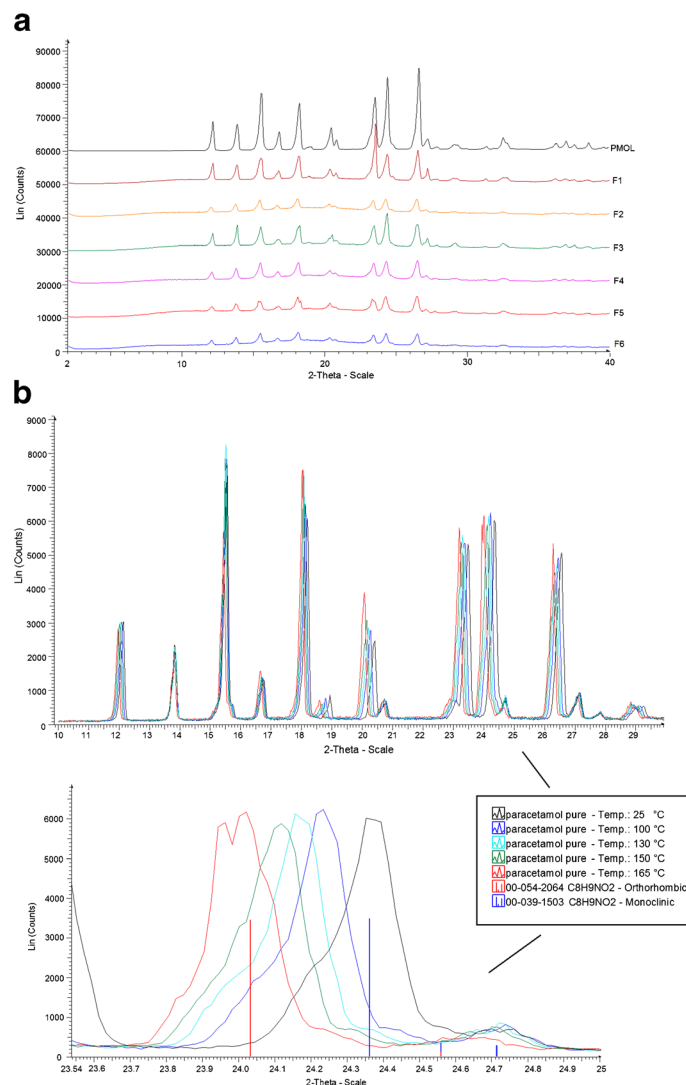


Fig. 5. **a** XRD diffractograms of PMOL and all binary formulations. **b** VTXRD diffractograms of sono-crystallised PMOL micro/nano crystals. **c** VTXRD diffractograms of PMOL/EPO binary systems. **d** VTXRD diffractograms of PMOL/S630 binary systems

The single X-ray crystallographic imaging revealed that the sono-crystallised PMOL existed as monoclinic form (21) and the details of the crystal structure are depicted in Fig. 4. The standard XRPD diffractogram of the monoclinic sono-crystallised PMOL form I showed characteristic peaks at 2θ values at 11.9–26.50 followed by a series less intense peaks at different 2θ values at ambient temperature (Fig. 5a). Similarly, various drug/polymer binary mixtures showed the characteristic diffraction peaks of PMOL with slightly lower intensity indicating that PMOL is present in its same form. Further analysis *via* a VT-XRPD analysis of crystallised PMOL clearly showed the characteristic peak of form I at 24.0 degree 2θ at ambient temperature (24) which started shifting as the temperature increased. This could be a sign of the crystalline structural change of the drug (*e.g.* a distorted lattice becoming less stable). This alteration of the monoclinic lattice increases with temperature up to 161°C (Fig. 5b). Thereafter, a slight temperature increase directed to the polymorphic transformation of paracetamol to its less stable form orthorhombic and completed at about 164–166°C (Fig. 5b). The signature diffraction peak for monoclinic form at 24.35 2θ shifted to a new position at 24.04 2θ confirming

the transformation of the monoclinic form to less stable form II.

Similar studies with the formulations with two polymers showed that regardless of the drug loadings, the signature peak at 24.36 2θ for monoclinic form starts shifting as a function of the applying temperature and the transformation was completed at about 112°C when the peak was positioned at 24.03 2θ with higher intensity corresponding to the orthorhombic structure (Fig. 5c). There was no obvious change observed upon increasing the temperature further up to 120°C. In contrast, the formulations of PMOL/S630 formulations (F4-F6) exhibited a transformation of PMOL at slightly higher temperature 120°C (Fig. 5d). This could be linked to the higher T_g (~105°C) of S630 polymer which may have resulted in the thermal stability to retain the crystal structure of the drug while heating. In the case of EPO, since the T_g was quite lower (~48°C), the transformations occurred at about 112°C. However, the polymorphic transformation occurring temperature for PMOL depended on the nature and thermal stability of the polymers used. It can be concluded that the VT-XRPD is a useful tool to study the temperature effects on the polymorphic transformation (25)

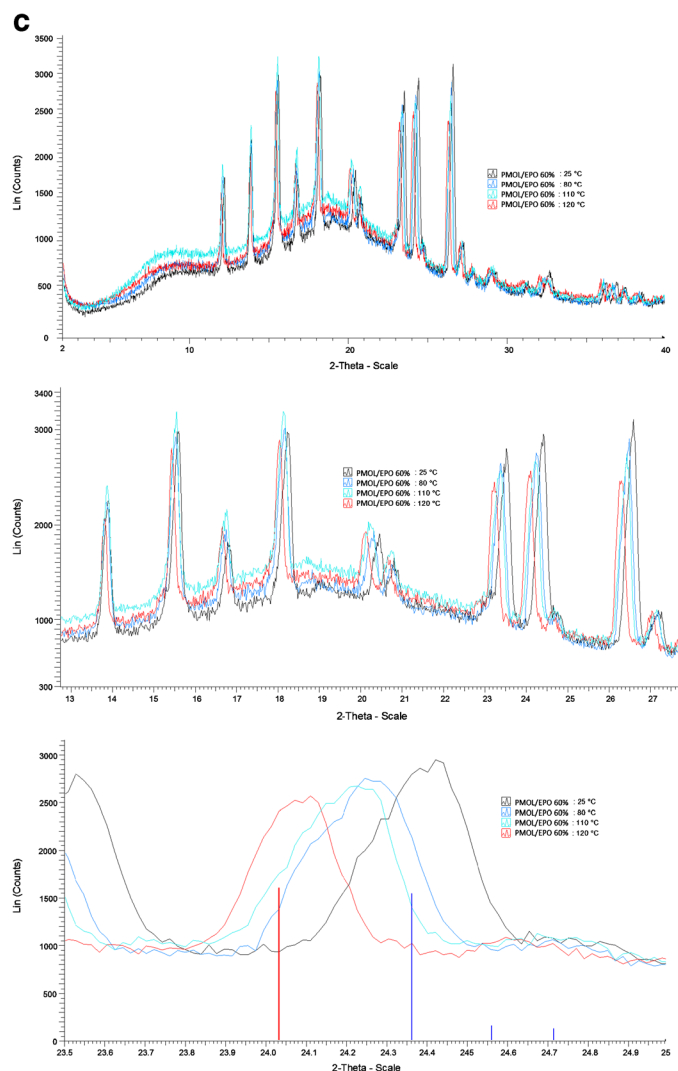


Fig. 5. continued.

of a crystalline drug. The thermal stability of a crystalline molecule is pivotal in terms of long-term product stability in pharmaceutical product manufacturing and development.

CONCLUSIONS

The calculated solubility parameters indicated the possible drug/polymer miscibility complemented by the results exhibited by thermal analysis. The approach adopted by the sono-crystallisation proved to be an effective technique to produce nano-micro sized crystals with high thermal stability. The temperature-assisted VTXRPD was successfully applied to study the alteration in the crystal structure of the sono-crystallised PMOL from various water soluble polymer matrices as a function of increasing the temperature. In this study, it has been seen that the polymorphic change was temperature dependant (at a range of 112–120°C) while the nature of the polymers played a vital role. In conclusion, VTXRPD can effectively be exploited as a useful approach to study possible polymorphic change of various drug candidates to develop different dosage forms. This is particularly suited to enhance the dissolution rates of poorly water soluble crystalline drugs or increasing physical/mechanical properties of various crystalline actives, e.g. paracetamol.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

- Hancock BC, Shalaev EY, Shamblin SL. Polyamorphism: a pharmaceutical science perspective. *J Pharm Pharmacol*. 2002;54:1151–2.
- Maniruzzaman M, Islam MT, Moradiya HG, Halsey S, Chowdhry BZ, Snowden MJ, *et al*. Prediction of polymorphic transformation of paracetamol in solid disersions. *J Pharm Sci*. 2014;103:1819–28.
- Sander JRG, Buc'ar DK, Baltrusaitis J, MacGillivray LR. Organic nanocrystals of the resorcinarene hexamer via sonochemistry: evidence of reversed crystal growth involving hollow morphologies. *J Am Chem Soc*. 2012;134:6900–3.
- Sinha B, Miller RH, Męschwitzer JP. Bottom-up approaches for preparing drug nanocrystals: formulations and factors affecting particle size. *Int J Pharm*. 2013;453:126–41.
- Merisko-Liversidge EM, Liversidge GG. Drug nanoparticles: formulating poorly water-soluble compounds. *Toxicol Pathol*. 2008;36:43–8.
- Wang M, Rutledge GC, Myerson AS, Trout BL. Production and characterization of carbamazepine nanocrystals by electrospraying for continuous pharmaceutical manufacturing. *J Pharm Sci*. 2012;101:1178–88.
- de Castro MD L, Priego-Capote F. Ultrasound-assisted crystallization (sonocrystallization). *Ultrason Sonochem*. 2007;14:717–24.
- Sander JRG, Zeiger BW, Suslick KS. Sonocrystallization and sonofragmentation. *Ultrason Sonochem*. 2014;21:1908–15.
- Suslick KS. Sonochemistry. *Science*. 1990;247:1439–45.
- Maniruzzaman M, Boateng JS, Bonnefille M, Aranyos A, Mitchell JC, Douroumis D. Taste masking of paracetamol by hot-melt extrusion: an in vitro and in vivo evaluation. *Eur J Pharm Biopharm*. 2012;80(2):433–42.
- Qi S, Avallé P, Saklatvala R, Craig DQM. An investigation into the effects of thermal history on the crystallisation behaviour of amorphous paracetamol. *Eur J Pharm Biopharm*. 2008;69:364–71.
- Qi S, Gryczke A, Belton P, Craig DQM. Characterisation of solid dispersions of paracetamol and Eudragit® E prepared by hot-melt extrusion using thermal, microthermal and spectroscopic analysis. *Int J Pharm*. 2008;354:158–67.
- Rastogi SK, Zakrzewski M, Suryanarayanan R. Investigation of solid-state reactions using variable temperature X-ray powder diffractometry I. Aspartame hemihydrates. *Pharm Res*. 2001;18:267–73.
- Rastogi SK, Zakrzewski M, Suryanarayanan R. Investigation of solid-state reactions using variable temperature X-ray powder diffractometry II. Aminophylline monohydrate. *Pharm Res*. 2002;19:1265–73.
- Maniruzzaman M, Islam MT, Moradiya HG, Halsey SA, Slipper IJ, Chowdhry BZ, *et al*. Prediction of polymorphic transformations of paracetamol in solid dispersions. *J Pharm Sci*. 2014;103(6):1819–28.
- Hansen CM. The universality of the solubility parameter. *Ind Eng Chem Res Dev*. 1969;8:2–11.
- Hoftyzer PJ, Krevelen DWV. Properties of polymers. Amsterdam: Elsevier; 1976.
- PDF-2 Release in Kabekkodu SN. International Centre for Diffraction Data: Newtown Square, PA, 2008.
- Maniruzzaman M, Pang J, Morgan DJ, Douroumis D. Molecular modelling as a predictive tool for the development of solid dispersions. *Mol Pharm*. 2015;12(4):1040–9.
- Zheng X, Yang R, Tang X, Zheng L. Part I characterization of solid dispersions of nimodipine prepared by Hot-melt extrusion. *Drug Dev Ind Pharm*. 2007;33:791–802.
- Buc'ar D-K, Elliott JA, Eddleston MD, Cockcroft JK, Jones W. Sonocrystallization Yields Monoclinic Paracetamol with Significantly Improved Compaction Behavior
- Barton JM. Dependence of polymer glass transition temperatures on heating rate. *Polymer*. 1969;10:151–4.
- Hancock B, Dalton C, Pikal M, Shamblin S. A pragmatic test of a simple calorimetric method for determining the fragility of some amorphous pharmaceutical materials. *Pharm Res*. 1998;15:762–7.
- Martino PD, Conflant P, Drache M, Huvenne JP, Guyot- Hermann AM. Preparation and physical characterization of forms II and III of paracetamol. *J Therm Anal Calorim*. 1997;48(3):447–58.
- De Villiers MM, Terblanche RJ, Liebenberg W, Swanepoel E, Dekker TG, Mingna S. Variable-temperature X-ray powder diffraction analysis of the crystal transformation of the pharmaceutically preferred polymorph C of mebendazole. *J Pharm Biomed Anal*. 2005;38:435–41.